REMARKS

Claim 5 is amended for grammatical reasons to include a comma. Claims 1-8 are pending and examined. No new matter is added.

Rejections Under 35 U.S.C. § 102(b)

Claim 1 is rejected under 35 U.S.C. § 102(b) as being anticipated by Schinazi *et al.* (U.S. Patent 5,703,058, referred to as "Schinazi '058"). The Office Action states that Schinazi '058 teaches

1) FTC for HBV at column 2, lines 40-41;

2) alpha interferon for HBV at column 2, lines 46-55;

3) and L-FMAU with the (-)enantiomer of FTC for HBV at column 6, lines 21-27.

Legal Standard For Anticipation

It is a well-established principle of patent law that to anticipate a claim, the reference must teach every element of the claim (see MPEP 2131.01). In other words, a "claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). The Federal Circuit has held that "[A]nticipation under § 102 can be found only when the reference discloses exactly what is claimed and that where there are differences between the reference disclosure and the claim, the rejection must be based on § 103 which takes differences into account." *Titanium Metals Corp. v. Banner*, 778 F.2d 775 (Fed. Cir. 1985). In addition, there can be no anticipation where the reference is so broad that the likelihood of arriving at the claimed composition would be the same as

discovering the combination of a safe by an inspection of its dials. *Ex parte Garvey,* 41 USPQ 583 (POBA 1939).

Schinazi '058 Fails to Disclose Exactly What Is Claimed

Applicants respectfully traverse the rejection of claim 1 on the basis that Schinazi '058 fails to disclose exactly what is claimed. In other words, in the passages cited by the Office Action, Schinazi '058 does not disclose a method for the treatment or prophylaxis of a human infected with hepatitis B virus comprising administering in combination or alternation an effective amount of 1) ß-L-FTC; 2) L-FMAU; and 3) interferon, or their pharmaceutically acceptable salts or prodrugs, independently optionally in pharmaceutically acceptable carriers.

In the first passage cited by the Office Action, Schinazi '058 states

> Both FTC and 3TC exhibit activity against HBV. Furman, *et al.*, "The Anti-Hepatitis B Virus Activities, Cytotoxicities, and Anabolic Profiles of the (-) and (+) Enantiomers of cis-5-Fluoro-1-[2-(Hydroxymethyl)-1,3-Oxathiolane-5-yl]Cytosine" *Antimicrobial Agents and Chemotherapy*, December 1992, page 2686-2692.

(Schinazi '058, col. 2, lines 39-45). The above passage discloses FTC, but the above passage **does not** disclose the combination or alternation of all three claimed components: 1) ß-L-FTC; 2) L-FMAU; and 3) interferon, or their pharmaceutically acceptable salts or prodrugs, independently optionally in pharmaceutically acceptable carriers.

In the second passage cited by the Office Action, Schinazi '058 states

> A human serum-derived vaccine has been developed to immunize patients against HBV. While it has been found effective, production of the vaccine is troublesome because the supply of human serum from chronic carriers is limited, and the purification procedure is long and expensive. Further, each batch of vaccine prepared from different serum must be tested in chimpanzees to ensure safety. Vaccines have also been produced through genetic

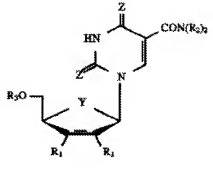
> engineering. Daily treatments with α-interferon, a genetically engineered protein, has also shown promise.

(Schinazi '058, col. 2, lines 46-55). The above passage discloses α-interferon, but the above passage **does not** disclose the combination or alternation of all three claimed components: 1) ß-L-FTC; 2) L-FMAU; and 3) interferon, or their pharmaceutically acceptable salts or prodrugs, independently optionally in pharmaceutically acceptable carriers.

In the third passage cited by the Office Action, Schinazi '058 states

> Nonlimiting examples of antiviral agents that can be used in combination with the compounds disclosed herein include the (-)-enantiomer of 2-hydroxymethyl-5-(5-fluorocytosin-1-yl)-1,3-oxathiolane (FTC); the (-)-enantiomer of 2-hydroxymethyl-5-(cytosin-1-yl)-1,3-oxathiolane (3TC); carbovir, acyclovir, interferon, famciclovir, penciclovir, AZT, DDI, DDC, L-(-)-FMAU, and D4T.

(Schinazi '058, col. 6, lines 21-27). The above passage individually discloses FTC, L-FMAU, or interferon, but the above passage **does not** disclose the combination or alternation of all three claimed components with each other as claimed in current claim 1. On the contrary, Schinazi '058 teaches that each of the compounds can individually be used in combination with the inventive compounds of the '058 patent- i.e., the compounds disclosed in columns 3, 4, and 5 of Schinazi '058, such as the compound of column 5, lines 12-22:

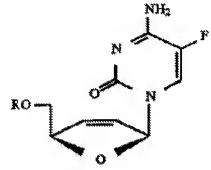


The text simply does not support a disclosure of the compounds with each other.

In response to Applicants' previous arguments, the Office Action states

> In response, the claim recites a composition that is in combination with β-L-FTC, L-(-) FMAU, and interferon. The word "and" in line 12 of the claim denotes that the agents are used in combination with each other. Further, the claim language *comprising* leaves the claim open for the inclusion of unspecified ingredients, even in major amounts and as such, does not exclude the composition of claim 1.

(Office Action, page 5, lines 14-19). As a matter of convenience, claim 1 of Schinazi '058 is presented as follows:

> 1. A composition comprising an effective HIV or HBV treatment amount of a compound of the formula:
>
> 
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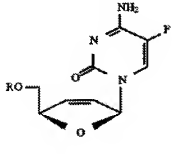
>
> wherein R is hydrogen, monophosphate, diphosphate, or triphosphate; in combination or alternation with a second compound selected from the group consisting of 2-hydroxymethyl-5-(5-fluorocytosin-1-yl)-1,3-oxathiolane, 2-hydroxymethyl-5-(cytosin-1-yl)-1,3-oxathiolane; 9-[4-(hydroxymethyl)-2-cyclopenten-1-yl]-guanine (carbovir), 9-[(2-hydroxyethoxy)methyl]guanine (acyclovir) interferon, 3'-deoxy-3'-azidothymidine (AZT), 2',3'-dideoxyinosine (DDI), 2',3'-dideoxycytidine (DDC), (-)-2'-fluoro-5-methyl-.beta.-L-ARAuridine (L-(-)-FMAU) and 2',3'-didehydro-2',3'-dideoxythymidine (D4T).

(Schinazi '058, col. 20, line 66 through col. 21, line 23). Applicants note that the claim actually states "**a second compound selected from the group consisting of**" at column 21, lines 13-14 of Schinazi '058. The statement in the Office Action that the word "and" in line 12 of the claim denotes that the agents are used in combination with each other is not consistent with well-established Markush practice (see MPEP 2173.05(h) for guidance with respect to USPTO policy

for interpretation of Markush groups). For example, the MPEP clearly indicates that the "and" at the end of a Markush group is equivalent to an "or" (see MPEP 2173.05(h) I). Notably, Schinazi '058 clearly discloses that the first compound (presented by the chemical structure) is to be combined with "a second compound" - not multiple compounds. In other words, Schinazi '058 discloses a two-component composition, where one of the components is a compound presented by the chemical structure, and a second compound from the list of compounds. While the Office Action argues that the word "comprising" leaves the claim open to additional components, such open-ended language is immaterial to what Schinazi '058 actually discloses, and is legally insufficient to support anticipation by Schinazi '058. In fact, the combination or alternation of the components with each other in a 3-component system has been supplied entirely by the Office Action in view of the present specification.

As is clearly shown in claim 1 of Schinazi '058, the cited reference teaches two component compositions, where one of the components is, for example, represented by a chemical formula such as 

. Schinazi '058 clearly fails to teach the combination or alternation of the three-component system as in the present claim 1. Therefore, Applicants respectfully request withdrawal of the rejection of claim 1 as anticipated by Schinazi '058.

Rejections Under 35 U.S.C. § 103(a)

Claims 1-8 are rejected under 35 U.S.C. § 103(a) as being anticipated by Schinazi et al (U.S. Patent 5,703,058, referred to as "Schinazi '058") and Thyagarajan (U.S. Patent 6,589,570).

The Office Action states that Schinazi '058 teaches

1) FTC for HBV at column 2, lines 40-41;

2) alpha interferon for HBV at column 2, lines 46-55;

3) and L-FMAU with the (-)enantiomer of FTC for HBV at column 6, lines 21-27.

The Office Action further states that Schinazi '058 does not teach the β-L-FTC is substantially pure, and it does not teach the many variations of interferon. The Office Action argues that regarding the substantially pure form of β-L-FTC, Schinazi '058 teaches that the β-L forms are specifically contemplated (column 7, line 64 to column 8, line 3). Applicants note that the passage cited by the Office Action states

> The antivirally active compounds disclosed herein are [5-carboxamido or 5-fluoro]-2',3'-dideoxy-2',3'-didehydro-pyrimidine nucleosides and [5-carboxamido or 5-fluoro]-3'-modified-pyrimidine nucleosides, in the racemic or β-D or β-L enantiomerically enriched form.

(Schinazi '058, column 7, line 64 to column 8, line 3). In this passage, Schinazi '058 is actually discussing the inventive compounds discussed at columns 3, 4, and 5, rather than the other non-inventive antiviral agents (*i.e.*, FTC and other compounds) described separately by Schinazi '058 at column 6, lines 21-27. The Office Action further argues that with respect to 90% weight ratios, differences in concentration will not support patentability unless there is evidence that such concentration is critical.

The Office Action argues that Thyagarajan teaches the use of alpha, beta and gamma interferon for the treatment of hepatitis B, and that Thyagarajan provides evidence that such

agents have been studied and are successful in the treatment of HBV infection, and that it would have been obvious to combine the teachings of Schinazi '058 and Thyagarajan due to the teaching by Thyagarajan of the successful treatment of HBV with alpha, beta and gamma interferon.

Legal Standard for Obviousness

U.S. case law holds that a proper obviousness inquiry requires four factual inquiries: (a) determining the scope and contents of the prior art; (b) ascertaining the differences between the prior art and the claims in issue; (c) resolving the level of ordinary skill in the pertinent art; and (d) evaluating evidence of secondary consideration. See *Graham v. John Deere*, 383 U.S. 1, 17-18, 148 USPQ 459, 467 (1966). Although the Supreme Court in *KSR* recently rejected a rigid application of the "teaching, suggestion, motivation" test, the Court did recognize that a showing of "teaching, suggestion, or motivation" to combine the prior art to meet the claimed subject matter could provide a helpful insight in determining whether the claimed subject matter is obvious under 35 U.S.C. § 103(a). See *KSR Int'l Co. v. Teleflex, Inc.*, No 04-1350 at 15 (U.S. Apr. 30, 2007). The Court further noted that an analysis supporting a rejection under 35 U.S.C. § 103(a) should be made explicit, and that "it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *KSR*, slip op. at 14. More recently, the Federal Circuit has explained that a flexible TSM test remains the primary guarantor against a non-statutory hindsight analysis. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007) ("[A]s the Supreme Court suggests, a flexible approach to the TSM test prevents hindsight and focuses on evidence before the time of invention."). The TSM test, flexibly applied, merely assures that the

obviousness test proceeds on the basis of evidence- teachings, suggestions, or motivations- that arise before the time of invention as the statute requires.

Therefore, Applicants respectfully traverse the rejection on the basis that 1) the combination of references fail to teach all of the claimed elements, 2) there is no motivation to combine the references, and 3) the references fail to provide a reasonable expectation of success. These factors provide a helpful insight in determining obviousness, and in view of these factors, the claims are not obvious under 35 U.S.C. § 103(a) from the combination of cited references.

The Cited References Fail to Teach Three Components Together

Applicants respectfully traverse the rejection of claims 1-8 on the basis that neither Schinazi '058 nor Thyagarajan teach three components together. In the passages cited by the Office Action, Schinazi '058 only teaches two components together.

In the first passage cited by the Office Action, Schinazi '058 states

> Both FTC and 3TC exhibit activity against HBV. Furman, *et al.*, "The Anti-Hepatitis B Virus Activities, Cytotoxicities, and Anabolic Profiles of the (-) and (+) Enantiomers of cis-5-Fluoro-1-[2-(Hydroxymethyl)-1,3-Oxathiolane-5-yl]Cytosine" *Antimicrobial Agents and Chemotherapy*, December 1992, page 2686-2692.

(Schinazi '058, col. 2, lines 39-45). The above passage discloses FTC, but the above passage **does not** teach the combination or alternation of all three claimed components: 1) ß-L-FTC; 2) L-FMAU; and 3) interferon, or their pharmaceutically acceptable salts or prodrugs, independently optionally in pharmaceutically acceptable carriers.

In the second passage cited by the Office Action, Schinazi '058 states

> A human serum-derived vaccine has been developed to immunize patients against HBV. While it has been found effective, production of the vaccine is troublesome because the supply of human serum from chronic carriers is limited, and the purification

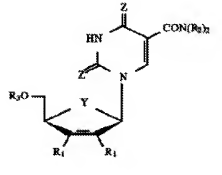
> procedure is long and expensive. Further, each batch of vaccine prepared from different serum must be tested in chimpanzees to ensure safety. Vaccines have also been produced through genetic engineering. Daily treatments with α-interferon, a genetically engineered protein, has also shown promise.

(Schinazi '058, col. 2, lines 46-55). The above passage discloses α-interferon, but the above passage **does not** teach the combination or alternation of all three claimed components: 1) ß-L-FTC; 2) L-FMAU; and 3) interferon, or their pharmaceutically acceptable salts or prodrugs, independently optionally in pharmaceutically acceptable carriers.

In the third passage cited by the Office Action, Schinazi '058 states

> Nonlimiting examples of antiviral agents that can be used in combination with the compounds disclosed herein include the (-)-enantiomer of 2-hydroxymethyl-5-(5-fluorocytosin-1-yl)-1,3-oxathiolane (FTC); the (-)-enantiomer of 2-hydroxymethyl-5-(cytosin-1-yl)-1,3-oxathiolane (3TC); carbovir, acyclovir, interferon, famciclovir, penciclovir, AZT, DDI, DDC, L-(-)-FMAU, and D4T.

(Schinazi '058, col. 6, lines 21-27). The above passage individually discloses FTC, L-FMAU, or interferon, but the above passage **does not** teach the combination or alternation of all three claimed components with each other as claimed in current claim 1. On the contrary, Schinazi '058 teaches that each of the compounds can individually be used in combination with the inventive compounds of the '058 patent- i.e., the compounds disclosed in columns 3, 4, and 5 of Schinazi '058, such as the compound of column 5, lines 12-22:



The text simply does not support a teaching of three compounds with each other.

In response to Applicants' previous arguments, the Office Action states

> In response, the claim recites a composition that is in combination with β-L-FTC, L-(-) FMAU, and interferon. The word "and" in line 12 of the claim denotes that the agents are used in combination with each other. Further, the claim language *comprising* leaves the claim open for the inclusion of unspecified ingredients, even in major amounts and as such, does not exclude the composition of claim 1.

(Office Action, page 5, lines 14-19). As a matter of convenience, claim 1 of Schinazi '058 is presented as follows:

> 1. A composition comprising an effective HIV or HBV treatment amount of a compound of the formula:
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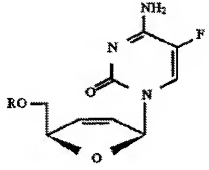
> 
>
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> wherein R is hydrogen, monophosphate, diphosphate, or triphosphate; in combination or alternation with a second compound selected from the group consisting of 2-hydroxymethyl-5-(5-fluorocytosin-1-yl)-1,3-oxathiolane, 2-hydroxymethyl-5-(cytosin-1-yl)-1,3-oxathiolane; 9-[4-(hydroxymethyl)-2-cyclopenten-1-yl]-guanine (carbovir), 9-[(2-hydroxyethoxy)methyl]guanine (acyclovir) interferon, 3'-deoxy-3'-azidothymidine (AZT), 2',3'-dideoxyinosine (DDI), 2',3'-dideoxycytidine (DDC), (-)-2'-fluoro-5-methyl-.beta.-L-ARAuridine (L-(-)-FMAU) and 2',3'-didehydro-2',3'-dideoxythymidine (D4T).

(Schinazi '058, col. 20, line 66 through col. 21, line 23). Applicants note that the claim actually states "**a second compound selected from the group consisting of**" at column 21, lines 13-14 of Schinazi '058. The statement in the Office Action that the word "and" in line 12 of the claim

denotes that the agents are used in combination with each other is not consistent with well-established Markush practice (see MPEP 2173.05(h) for guidance with respect to USPTO policy for interpretation of Markush groups). For example, the MPEP clearly indicates that the "and" at the end of a Markush group is equivalent to an "or" (see MPEP 2173.05(h) I). Notably, Schinazi '058 clearly discloses that the first compound (presented by the chemical structure) is to be combined with "a second compound" - not multiple compounds. In other words, Schinazi '058 teaches a two-component composition, where one of the components is a compound presented by the chemical structure, and a second compound from the list of compounds. While the Office Action argues that the word "comprising" leaves the claim open to additional components, such open-ended language is immaterial to what Schinazi '058 actually positively teaches, and is legally insufficient to support obviousness without hindsight reconstruction of the Applicants' own disclosure. In fact, the combination or alternation of the components with each other in a 3-component system has been supplied entirely by the Office Action in view of the present specification.

Thyagarajan fails to remedy the deficiencies of Schinazi '058. Thyagarajan clearly fails to teach the three components as instantly claimed. Table 1 of Thyagarajan merely states that certain individual agents have been studied in the treatment of HBV infection.

The References Fail to Provide a Motivation to Combine

The Office Action relies on Thyagarajan as teaching that interferons are successful at treating HBV, and therefore it would have been obvious to combine them with the teachings of Schinazi '058. However, Thyagarajan actually characterizes the interferons as having "limited success rate, prohibitive cost, profound side effects" and also as being non-accessible (see

Thyagarajan, col. 2, lines 42-44). Thyagarajan concludes that it is necessary to search for newer agents for treatment of HBV infection. When taken as a whole, the Thyagarajan reference relied upon by the Office Action teaches away from the use of interferons individually, and provides no motivation whatsoever to add interferons to other combinations. In fact, Thyagarajan specifically teaches that such compounds should not be used, but rather newer antihepatitis B agents should be developed (see col. 2, lines 44-46).

The References Fail to Provide a Reasonable Expectation of Success

The Office Action relies on Thyagarajan providing a reasonable expectation of success, apparently on the theory that interferons are successful at treating HBV, and therefore it would have been obvious to combine them with the teachings of Schinazi '058. However, there is nothing in Thyagarajan to suggest that interferons can be combined with any and all treatments to retain any effectiveness. In fact, Thyagarajan actually teaches away from the use of interferons. Thyagarajan actually characterizes the interferons as having "limited success rate, prohibitive cost, profound side effects" and also as being non-accessible (see Thyagarajan, col. 2, lines 42-44). Thyagarajan concludes that it is necessary to search for newer agents for treatment of HBV infection. When taken as a whole, the Thyagarajan reference relied upon by the Office Action teaches away from the use of interferons individually, and provides no expectation for success in combining interferons with other components. Simply put, the Office Action provides no basis in the literature for expecting that interferons can be combined with anything, particularly where the art cited by the Office Action actually teaches that interferons have limited success rates, prohibitive costs, and profound side effects. In fact, Thyagarajan specifically teaches that such compounds should not be used, but rather newer antihepatitis B agents should

be developed (see col. 2, lines 44-46). In addition, nothing in Schinazi '058 provides any reasonable expectation of success in combining or alternating the three components as claimed.

In summary, i) neither reference teaches the combination or alternation of the required three components with each other, ii) Thyagarajan teaches away from the use of interferons, and iii) the Office Action relies on improper hindsight reconstruction with no reasonable expectation of success. Therefore, Applicants respectfully request withdrawal of the rejection.

CONCLUSION

Based on the foregoing amendments and remarks, Applicants respectfully request reconsideration and withdrawal of the rejection of claims and allowance of this application.

AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for consideration of this Amendment to Deposit Account No. **50-3732**, Order No. 04674.105074 (TRI 1016).

In the event that an extension of time is required, or which may be required in addition to that requested in a petition for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. **50-3732**, Order No. 04674.105074 (TRI 1016).

Respectfully submitted,
King & Spalding, LLP

Dated: September 16, 2008 By: /michael willis/
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